Ventricular Wall Stress Revisited
A Keystone of Cardiology

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SUMMARY
Wall stress has been used as one of the parameters of myocardial mechanics. The present review focuses on recently developed data on ventricular wall stress, especially in relation to other newly developed areas in cardiology. In hypertensive hearts, there is a broad continuous spectrum in the structural and functional changes: those with low wall stress (inappropriate hypertrophy), those with normal wall stress (appropriate hypertrophy) and those with high wall stress (inadequate hypertrophy). Among them, the responses to neurohumoral stimuli are various, and their clinical features and courses also varied. These differences in wall stress among the different categories of hypertensive hearts may be caused by the variable influences of non-mechanical factors, such as molecular, metabolic and neurohumoral ones. Wall stress is an essential determinant of myocardial oxygen consumption, and is also an important determinant of the myocardial contractile state and diastolic function. In contrast to excitation-contraction coupling, contraction-excitation feedback has been studied, suggesting the importance of wall stress regulating electrical phenomena. The interrelationship between mechanical factors (including wall stress) and non-mechanical factors (including molecular, metabolic, neurohumoral and genetic ones) has been investigated intensively. In conclusion, wall stress (or force on the myocardial cell) may be a keystone in cardiology, relating to each of the cardiac phenomena. If wall stress deviates from the normal range, even with compensatory mechanisms, severe cardiac events occur. The compensatory mechanisms for wall stress may act as a risk factor on the heart, especially when the wall stress remains outside the normal range. (Jpn Heart J 35: 577–587, 1994)

Key words: Left ventricular hypertrophy Mechanical factor Non-mechanical factor Myocardial oxygen consumption Left ventricular mechanics Contraction-excitation feedback Molecular Metabolic changes Neurohumoral factors Genetic system
Wall stress is the force per unit cross-sectional area. It is a macroscopic concept, and may correspond to force on the single myocardial cell, which is a microscopic one.

In 1892, Woods, using post-mortem specimens, demonstrated that Laplace’s law could be applied to the heart to calculate wall tension. In the 1950s, following the development of analysis of X-ray images of the contrast-filled left ventricle, ventriculography developed into a method for quantitative evaluation of left ventricular (LV) function in animals and then in man. In 1963, Sandler and Dodge calculated peak systolic LV wall stress by LV pressure observations and measurement of LV dimensions and wall thickness made from biplane angiocardiograms. Since then, many attempts have been made to evaluate wall stress, from both theoretical and technical (including echocardiographic) approaches. Cardiologists, physiologists and engineers have long been interested in wall stress, mainly from the viewpoints of mechanics, using the force-velocity relationship.

Since the 1980s, cardiac mechanics have mainly been studied using the theory of the end-systolic pressure-volume relationship. In addition, molecular biology has become one of the main areas of focus in cardiology.

The present review will focus on recent information about ventricular wall stress, especially in relation to other newly developed categories in cardiology.

**LV Hypertrophy (LVH)**

In 1960, Linzbach postulated that “hypertrophy increases until the force generated per cross-sectional unit [of ventricular wall] returns to normal values”. There were, however, only a few studies focusing on this point. In 1963, Sandler and Dodge calculated peak systolic LV wall stress in 2 patients with aortic stenosis, finding values similar to, or less than, those in 3 patients without ventricular hypertension. In 1965, Grant et al observed that in patients with volume overload the ratio between LV wall thickness and chamber radius at end-diastole was not different from the normal ratios. They theorized that stress was therefore normalized. In 1968, Hood et al defined normal ranges for end-diastolic and peak systolic wall stress in 6 subjects with LV diseases, and found that peak systolic wall stress was not significantly greater than normal in 18 patients with compensated volume overload and 1 patient with compensated pressure overload, but was increased in 4 patients with decompensated pressure or volume overload.

Development of echocardiographic methods made it possible to measure LV wall thickness which had increased due to hypertrophy of myocytes by a parallel alignment of sarcomeres. Since then, many investigators have been
interested in LVH evaluated echocardiographically in essential hypertension, probably because epidemiologic data have indicated that LVH is a serious risk factor for cardiovascular events. The introductions of most of these papers concerning LVH in hypertension begin with the sentence, "LVH is a structural adaptation of the heart to sustained hypertension, serving to normalize systolic wall stress." However, there have been almost no papers indicating the evidence of normalization of systolic wall stress in hypertension.

Between clinical systolic blood pressure and LV mass, only relatively weak correlations ($r = 0.20-0.45$) exist. Slightly closer relations exist between the average of multiple blood pressure measurements made over many years and LV mass. Better prediction of LV mass is achieved for pressures measured during normal activity by ambulatory monitoring. However, the correlations between blood pressure and LV mass reach maximum values of $r = 0.50-0.60$, suggesting that no more than 25–35% of LV mass variability can be predicted (and even less may be caused) by the level of blood pressure.

In 1988, we showed that LV wall stress was not always normalized in patients with hypertensive hypertrophy without heart failure. Fifty-seven hypertensive patients with increased LV mass without LV dilatation were divided into 2 groups: i) 19 patients with subnormal end-systolic wall stress ($<2SD$ below the normal mean) (Group I) and 38 patients with normal end-systolic wall stress (within 2SD of the normal mean) (Group II). Group II was divided into 2 subgroups: 25 patients with slightly increased LV mass (up to twice the normal mean) (Group IIA) and 13 patients with severely increased LV mass (more than twice the normal mean) (Group IIB). The inotropic response to isoproterenol was significantly greater in Group I than in Group IIA, and in Group IIA compared to Group IIB. The latter had higher plasma noradrenaline concentrations than Groups I and IIA. We concluded that in patients with hypertension with subnormal end-systolic wall stress (inappropriate hypertrophy) the beta adrenergic response was increased, and that in hypertensive hypertrophy with normal wall stress (appropriate hypertrophy) it was normal or became reduced as plasma noradrenaline increased. Compared to those with LVH, the response was less in the hypertensive patients without LVH, and was much less in those with LV dilatation (high wall stress). Responses to noradrenaline were also different between those with LVH and those without. These findings may correspond to both experimental and human observations suggesting the stimulation of cardiac hypertrophy by neurohumoral factors, such as the sympathetic nervous system and renin-angiotensin system.

In our recent study, patients with isolated systolic hypertension without heart failure were compared to normal controls. The patients were composed of mainly elderly patients and some with aortitis syndrome. The patients had signifi-
cantly larger LV mass and higher LV end-systolic wall stress than the normal controls. These findings might suggest that high end-systolic wall stress from systolic hypertension can not be normalized. This might correspond to the fact that there is a close correlation between diastolic blood pressure and LV mass, as diastolic hypertension may be more regulated by neurohumoral factors than is systolic hypertension.

Many studies have shown the different effects of antihypertensive treatment on regression of LVH in hypertension. However, cardiac determinants of the regression of LVH in hypertension with antihypertensive treatment have not been studied. In our follow-up study\textsuperscript{18} of patients with hypertensive LVH with subnormal end-systolic wall stress (inappropriate hypertrophy, probably induced by a neurohumoral factor) (Group I), a decrease in blood pressure with antihypertensive treatment did not lead to regression of LVH, but rather to an increase in LV mass. In patients with normal end-systolic wall stress (appropriate hypertrophy, probably induced by high arterial pressure) antihypertensive treatment decreased LV mass if it had sufficient potency to cause regression of the myocardium.

As described above, even if a mechanical factor such as chronic pressure overload was at the same level, LV changes in hypertension might be variable, probably due to the different influences of non-mechanical factors. As shown in Figure 1\textsuperscript{15}, non-mechanical factors have a variety of effects, from acceleration of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Schematic diagram of the possible roles of mechanical and non-mechanical factors in the etiology of hypertensive hearts, in comparison with hypertrophic cardiomyopathy and dilated cardiomyopathy. (NS: nervous system) (from Sugishita et al\textsuperscript{15})}
\end{figure}
LVH to inhibition of LVH (= dilatation), causing a broad spectrum of clinical features in hypertensive hearts. When there is no non-mechanical factor, as shown in the center of Figure 1, the mechanical factor induces appropriate hypertrophy (Group IIA), which progresses to severe LVH (Group IIB) and to heart failure. When there is a non-mechanical factor which increases LVH, inappropriately hypertrophy is induced (Group I), which has clinical features similar to hypertrophic cardiomyopathy. When there is a non-mechanical factor inhibiting LVH or aggravating dilatation, it does not cause LVH but rather dilatation, which is similar to dilated cardiomyopathy. The location on the axis of the abscissa in Figure 1 may be determined by the value of LV end-systolic wall stress, which has been modified by non-mechanical factors.

Recently, hypertensive LVH has been emphasized to be a risk factor for arrhythmias, coronary artery disease, congestive heart failure and sudden death. However, we think that this is not uniform throughout all categories of hypertensive LVH, but that it depends on the type of hypertensive LVH, especially as classified by LV end-systolic wall stress.

We followed 125 patients with hypertensive heart diseases for 4.4 ± 1.7 years. Table I shows the mortality rate and causes of death in each group. Mortality rate was high in Group D (dilatation, high stress) and Group I (LVH with low stress). This suggests that LVH with abnormal wall stress is a risk factor in LVH. Koren et al showed morbid and fatal events in hypertensive patients were high in those with eccentric or concentric LVH.

Recent studies suggest that the stimuli to cause LVH may be stroke volume, obesity, sodium intake and so on. Other non-mechanical factors will be discussed later.

We have shown that patients with dilated cardiomyopathy survive to an older age if LV wall thickness tends to increase, and that those with hypertrophic cardiomyopathy survive to an older age if LV diameter tends to increase slightly. These observations may suggest that normalization of LV wall stress may be beneficial to survival.

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**Table I. Deaths of Hypertensive Patients during Follow-up (4.4 ± 1.7 years)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Followed cases</th>
<th>Dead cases</th>
<th>Mortality rate (%)</th>
<th>Causes of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Inappropriate hypertrophy)</td>
<td>21</td>
<td>2</td>
<td>(10)</td>
<td>Renal failure, Other disease</td>
</tr>
<tr>
<td>II (Appropriate hypertrophy)</td>
<td>49</td>
<td>2</td>
<td>(4)</td>
<td>Other disease</td>
</tr>
<tr>
<td>Hypertrophy (−)</td>
<td>36</td>
<td>0</td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td>D (Dilatation)</td>
<td>19</td>
<td>5</td>
<td>(26)</td>
<td>Sudden death, Arrhythmia, Heart failure + arrhythmia, Arrhythmia, Other disease</td>
</tr>
</tbody>
</table>

(from Sugishita et al)

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MYOCARDIAL OXYGEN CONSUMPTION

In 1958, Sarnoff et al. suggested that myocardial oxygen consumption may be determined by five factors: basal state, electrical activity, internal work (wall stress × heart rate), external work (pressure × flow) and myocardial contractility, and suggested that wall stress may be one of the primary determinants. But quantitative analyses of these determinants were not performed. In 1983, Strauer showed a significant linear correlation between LV systolic wall stress and myocardial oxygen consumption/100 g myocardium.

We showed depressed coronary reserve and exercise-induced ST depression in patients with isolated systolic hypertension without coronary stenosis. This may be interpreted to be caused by increased myocardial oxygen consumption due to elevated LV end-systolic wall stress, as mentioned above. Recently, myocardial ischemia in patients with angiographically normal coronary arteries has been an issue in clinical cardiology. There might be, of course, various mechanisms for this condition, but the increase of myocardial oxygen consumption caused by increased wall stress may be one of the triggers of this phenomenon.

LV MECHANICS

In the 1960s and 1970s, the study of LV mechanics focused on the theory of force-velocity relationship, using myocardial shortening velocity and LV systolic wall stress. Since the 1980s, the end-systolic pressure-flow relationship has been the main trend in studying LV mechanics. In these studies, end-systolic wall stress may sometimes be used for end-systolic pressure.

The relationship between ejection phase index and afterload index also indicates the contractile state. For this purpose fractional shortening and end-systolic wall stress are often used, as these parameters are easily obtained echocardiographically. In hypertensive LVH this shows a linear relationship, and is used for the evaluation of changes of the LV contractile state after treatment. Effects of vasodilator therapy in congestive heart failure are also easily described using these axes.

Diastolic function has been described by the strain-stress relationship in experimental studies. End-diastolic wall stress is a parameter of preload.

It is known that diastolic function is depressed in LVH although systolic function is preserved. We studied diastolic function echocardiographically in 2 groups of patients with hypertensive LVH, classified by LV end-systolic wall stress. Those with inappropriate hypertrophy (low stress) had relatively diminished diastolic velocity before and during isoproterenol infusion, and those with appropriate hypertrophy (normal stress) had absolutely diminished velocity dur-
ing the infusion, in spite of having had normal diastolic velocity before the infusion.

**Electrical Phenomenon**

Excitation contraction coupling is the usual electrical phenomenon in the heart. However, changes in the amount of force acting on the myocardium have been shown to precede or cause changes in repolarization in isolated muscle. \(^{25}\) Changes in mechanical conditions, such as preload, contractility and afterload, can also influence the refractory period in an intact heart. \(^{27}\) This phenomenon has been termed “contraction-excitation feedback”. \(^{28}\) These changes in mechanical conditions of the myocardium may affect wall stress on the myocardium, or the force on a single myocardial cell. The mechanism of this phenomenon has been described as follows: the changes in myocardial conditions produce changes in distribution of intracellular calcium. Recently these changes have been explained as resulting from changes in ion channels, especially stretch activated channels. \(^{29}\) Calcium-influx was also increased by stretch. \(^{30}\)

We found that shortening of ejection time in patients with renal failure undergoing hemodialysis caused elongation of the QT interval, \(^{31}\) and we also found that the Valsalva maneuver shortened ejection time with elongation of the QT interval in normal controls. In contrast, shortening of the QT interval in patients with congestive heart failure has been observed (personal communication).

We found that giant negative T waves are often seen in hypertensive patients with inappropriate hypertrophy (low stress); high voltage with ST-T changes in those with appropriate hypertrophy (normal stress) with severe LVH; and high voltage in those with appropriate hypertrophy with mild LVH; and normal ECG in those without LVH. \(^{32}\) When the shortening of LV myocardium was accentuated in those with giant negative T waves, the depth of the T wave decreased. \(^{33}\) This change might also be explained by contraction-excitation feedback.

These ECG changes might be related to changes in wall stress (or force) affecting electrical phenomenon, and these changes might be arrhythmogenic. It has been suggested that increased ventricular systolic wall stress may be an essential determinant of the inducibility of sustained ventricular tachycardia. \(^{34}\) These arrhythmias may cause cardiac sudden death.
Molecular, Metabolic, Neurohumoral and Genetic Changes

There are many types of non-mechanical factors including molecular, metabolic, neurohumoral and genetic systems. The sympathetic nervous system, including alpha- and beta-adrenergic receptors, has been studied intensively, and recently the renin-angiotensin system has been highlighted.

Firstly, mechanical stimuli, mainly an increase in wall stress, induce changes in molecular, metabolic, neurohumoral and genetic systems, and induce LVH. Following chronic pressure overload in mammalian heart muscle, a decrease in maximum unloaded shortening velocity (Vmax) and/or a decrease in myosin adenosine triphosphatase (ATPase) activity, and isomyosin shift have been described. Work overload-induced hypertrophy induces a myosin heavy chain (MHC) transition from the normal adult (α-MHC) to the fetal (β-MHC) isoform that correlates with the changes in contractility detected in this model. In a recent study, the principal localization of the increase in insulin-like growth factor I to the subendocardial layer of the left ventricle suggested that wall stress was the most probable initiating stimulus for the enhanced synthesis of insulin-like growth factor I.

Secondly, the primary changes in molecular, metabolic, neurohumoral and genetic systems themselves, on the contrary, can induce LVH and decrease wall stress. These changes determine the location on the axis of the abscissa in Figure 1. These non-mechanical factors might be regulated by the genetic disposition, as Jackson et al. found that transgenic mice with an additional copy of the c-myc proto-oncogene had larger hearts than normal mice. In our study of hypertensive patients, there was a tendency for the inotropic reaction to isoproterenol infusion to be increased in the progenies of hypertensive patients with LVH compared to those of hypertensive patients without LVH, especially in those with inappropriate hypertrophy.

Many investigators have found various factors which cause LVH in vitro. However, it is necessary to know what induces LVH in situ.

Relationship between Wall Stress and Other Cardiac Parameters

LV wall stress or force on a single myocardial cell is related to each of the other cardiac phenomena (Figure 2). As summarized in Table II, changes (increase or decrease) in LV wall stress influence all other cardiac phenomena. This might be a special characteristic of the heart, which ejects blood continuously, in contrast to other organs in the intact body.
**Table II.** Influence of Wall Stress on the Other Cardiac Phenomena

<table>
<thead>
<tr>
<th>Wall stress</th>
<th>Normal</th>
<th>↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic function</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Afterload</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Ejection phase index</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Diastolic function</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Myocardial O₂ consumption</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-T changes</td>
<td>(Giant negative T)</td>
<td></td>
</tr>
<tr>
<td>Repolarization duration</td>
<td>↑ → Arrhythmia?</td>
<td>↓</td>
</tr>
<tr>
<td>Neurohumoral (Plasma noradrenaline ↑)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular</td>
<td></td>
<td>ATPase ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myosin heavy chain transition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertrophy ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk factor?</td>
</tr>
</tbody>
</table>

↑: increase, ↓: decrease
CONCLUSION

1) LV wall stress (or force on myocardial cell) may be a keystone of cardiology, relating to all cardiac phenomena. Stress itself is also modified by neurohumoral factors or genes.

2) If LV wall stress deviates from the normal range, even under compensatory mechanisms, severe cardiac events will occur.

3) The compensatory mechanisms for wall stress may act as a risk factor (causing arrhythmias, coronary artery disease, congestive heart failure, and sudden cardiac death), especially when wall stress remains in the abnormal range.

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